REMARKS

Claims 89-109 are pending and under examination. New claims 110-117 have been added. Support for the new claims can be found throughout the specification and claims as filed. In particular, support for new claims 89-98 can be found in the original claims and, for example, on page 9, lines 26-30, and page 10, lines 29-32. Accordingly, these new claims do not raise an issue of new matter and entry thereof is respectfully requested.

The rejection of claims 89-109 under 35 U.S.C. § 103 as allegedly obvious over Froesch et al., Proc. Am. Assoc. Cancer Res. 89:13 (1998), in view of Takayama et al., Cancer Res. 58:3116-3131 (1998), Noordzij et al., J. Urology 158:1880-1885 (1997) and Sano et al., U.S. Patent No. 5,665,539, is respectfully traversed. Applicant respectfully submits that the claimed methods are unobvious over Froesch et al., alone or in combination with Takayama et al., Noordzij et al., and/or Sano et al.

Applicant respectfully maintains, as discussed in the response filed May 2, 2006, that Froesch et al. does not teach or suggest methods for determining the risk of tumor recurrence or spread or for determining prognosis of survival in a patient suffering from prostate cancer by determining BAG-1 gene expression. At best, Froesch et al. describes the observation that BAG-1L is expressed in prostate cancers and enhances androgen receptor function. However, Froesch et al. provides no teaching or suggestion that the level of BAG-1 gene expression can be used to determine the risk of tumor recurrence or spread or for determining prognosis of survival in a patient suffering from prostate cancer by determining BAG-1 gene expression. Absent such a teaching or suggestion, Applicant respectfully submits that Froesch et al. cannot render the claimed methods obvious.

Furthermore, Takayama et al. does not cure the deficiencies of Froesch et al. Takayama et al., at best, describes expression of BAG-1 and BAG-1 variants in normal tissues and various tumor cell lines but provides no teaching or suggestion of methods for determining the risk of tumor recurrence or spread or for determining prognosis of survival in a patient suffering from prostate cancer by determining BAG-1 gene expression. The Office Action on page 5 refers to various descriptions in Takayama et al., but such descriptions provide no teaching or suggestion of using BAG-1 gene expression for determining the risk of tumor recurrence or spread or for

determining prognosis of survival in a patient suffering from prostate cancer. The Office Action asserts that Takayama et al. describes BAG-1 as consistently the most abundant form of BAG-1 expressed in tumors, which is merely a statement of which of the three forms of BAG-1 analyzed was predominantly expressed but provides no teaching or suggestion that BAG-1 expression can be used for determining the risk of tumor recurrence or spread or for determining prognosis of survival in a patient suffering from prostate cancer. In addition, the Office Action asserts that Takayama et al. describes that prostate cancer, breast cancer and leukemia cell lines were the most consistent expressors of BAG-1L, but this is merely a statement that the BAG-1L form is expressed more predominantly in prostate cancer, breast cancer and leukemia cell lines and again provides no teaching or suggestion that BAG-1 expression can be used for determining the risk of tumor recurrence or spread or for determining prognosis of survival in a patient suffering from prostate cancer. In fact Takayama et al. indicates that breast, colon and leukemia cell lines had consistently higher relative levels of 36-kDa BAG-1 protein expression but provides no teaching or suggestion that BAG-1 expression can be used for determining the risk of tumor recurrence or spread or for determining prognosis of survival in a patient suffering from prostate cancer.

Moreover, Noordzij et al. further cannot cure the deficiencies of Froesch et al., alone or in combination with Takayama et al. The Office Action asserts that Noordzij et al. describes determining the level of oncoprotein Bcl-2 and androgen receptor expression in pretreatment transurethral resection specimens of hormonally treated prostate cancer patients and correlating the results with tumor stage and grade and with the occurrence of clinical progression or tumor related death. However, Noordzij et al. found no correlation with Bcl-2. "The bcl-2 scores did not correlate with tumor stage or grade" (abstract). Noordzij et al. further indicates that "[A]ndrogen receptor scores were marginally related to tumor grade, but not to tumor stage" (abstract). Noordzij et al. states that a "prognostic value of bcl-2 or androgen receptor in pretreatment transurethral resection specimens was not found" (see abstract and page 1883, right column, first complete paragraph). Noordzij et al. found only a combined bcl-2/androgen receptor score to be an independent prognostic marker to predict clinical progression (see abstract and page 1883, right column, third paragraph). Sano et al. is alleged to teach detection of a protein using immuno-PCR.

Applicant respectfully disagrees with the assertion in the Office Action that it would have been *prima facie* obvious to one skilled in the art to determine the level of BAG-1 expressed in prostate cancer using immuno-PCR, compare the level with a reference level and further correlate the results with the risk of tumor recurrence, tumor spread and survival in a patient suffering from prostate cancer in view of the teachings of Froesch et al., Takayama et al., Noordzij et al. and/or Sano et al. To establish a *prima facie* case, the Office must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. See *Karsten Mfg. Corp. v. Cleveland Gulf Co.*, 242 F.3d 1376, 1385, 58 U.S.P.Q.2d 1286, 1293 (Fed. Cir. 2001); *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998); *Northern Telecom v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, a hindsight analysis is not allowed. See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); *In re Erlich*, 3 U.S.P.Q.2d 1011, 1016 (Bd. Pat. App. & Int. 1986). Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. See *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Applicant respectfully maintains that the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness, which requires that the prior art references relied upon give rise to the requisite motivation to combine their content, that when viewed in combination, provide the skilled person with a reasonable expectation of success to achieve the claimed invention, and that the combination of references teaches or suggests all limitations of the claims. Applicant respectfully submits that there would have been no motivation to combine the cited references. The Office Action asserts that one would have been motivated to combine the references because Froesch et al. describes BAG-1 protein as being expressed in 9/9 prostate cancer cell lines and 51/51 prostate tumor specimens, that BAG-1L protein is expressed in prostate cancers and enhances androgen receptor function, Takayama et al. describes BAG-1 protein as binding to bcl-2 and regulating apoptosis and overexpression of BAG-1 has been shown to increase the metastatic potential of tumor cells *in vivo*, and Noordzij

et al. describes that a combined bcl-2/androgen receptor score acts as an independent prognosticator for clinical progression. However, Applicant sees no basis for the assertion that these descriptions in the various references would have provided any motivation to combine them. To the contrary, Applicant respectfully submits that one skilled in the art would have had no motivation to combine these references to achieve the claimed methods. For example, the Office Action on page 6 indicates that Froesch et al. describes enhancement of androgen receptor function by BAG-1L and that Takayama et al. describes binding of BAG-1 to bcl-2 and regulation of cell apoptosis. In Takayama et al. (page 3117, left column, second complete paragraph), BAG-1 is described as augmenting the bioactivities of several proteins, including Bcl-2. Yet Noordzij et al. describes that there is no correlation with Bcl-2 or androgen receptor for prognosis of prostate cancer (see abstract and page 1883, right column). Furthermore, Noordzij et al. indicates that only a combined Bcl-2/androgen receptor score was prognostic, with those having low or high expression of both antigens (Bcl-2 negative, androgen receptor low or Bcl-2 positive, androgen receptor high) having a better prognosis than the other patients (Bcl-2 negative, androgen receptor high or Bcl-2 positive, androgen receptor low)(page 1882, left column). Froesch et al. describes enhancement of androgen receptor function by BAG-1L but provides no comment on androgen receptor levels, as measured in Noordzij et al. Takayama et al. describes augmenting the bioactivity of Bcl-2 by BAG-1. Even if, *arguendo*, one were to combine these references, there would have been no reasonable expectation of success because, based on the combination of references, there would be no way to predict whether BAG-1 expression above a reference level correlates with an increased risk or below a reference level correlates with a decreased risk of tumor recurrence or spread or survival in a prostate cancer patient, particularly in light of Noordzij et al.

Furthermore, the combination of these references provides no teaching or suggestion of the claimed methods. None of the cited references, alone or in combination, teaches or suggests a method for determining the risk of tumor recurrence or spread or survival of a patient suffering from prostate cancer by determining BAG-1 gene expression and comparing the BAG-1 gene expression level to a reference level, where an expression level above the reference level correlates with an increased risk of tumor recurrence or spread or survival and where an expression level below the reference level correlates with a decreased risk of tumor recurrence or spread or survival. Thus, Applicant respectfully submits that none of the three requirements

have been satisfied with respect to establishing a *prima facie* case of obviousness, let alone the necessary establishment of all three requirements.

As discussed above, Applicant respectfully submits that a *prima facie* case of obviousness has not been established. Applicant respectfully submits that Froesch et al., alone or in combination with Takayama et al. and/or Noordzij et al. and/or Sano et al. does not teach or suggest Applicant's claimed methods. Absent such a teaching or suggestion, Applicant respectfully submits that the claimed methods are unobvious over Froesch et al., alone or in combination with Takayama et al. and/or Noordzij et al. and/or Sano et al. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

In light of the remarks herein, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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